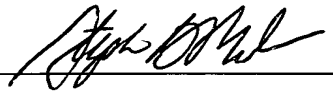
REMARKS

Attached herewith is a copy of Exhibit I (Mukaiyama et al., Chemistry Letters, pp. 615-618, 1984) which was referenced on page 11 and inadvertently omitted from the Amendment and Reply filed March 30, 2009.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date April 2, 2009

By 

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264

CHEMISTRY LETTERS, pp. 615 - 618, 1984.

A NOVEL ACID-RESISTANT ACETAL-TYPE PROTECTIVE GROUP FOR ALCOHOLS

Teruaki MUKAIYAMA,* Masahiro OHSHIMA,
Hitoshi NAGAOKA, and Masahiro MURAKAMI
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

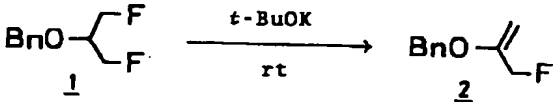
Alcohols are protected on treatment with 2-benzyloxy-3-fluoro-1-propene in the presence of a catalytic amount of $PdCl_2(COD)$, and the resulting acetals are easily deprotected to regenerate the parent alcohols by catalytic hydrogenation. The acetals, the protected alcohols, are rather resistant to acidic hydrolysis in comparison with common acetals because of the presence of fluoromethyl group.

In the preceding communication,[1] we have reported on a novel acetal-type protective reagent for hydroxyl groups, 2-benzyloxy-1-propene, with which both protection and regeneration of alcohols are achieved under mild conditions. Generally an acetal is readily hydrolyzed in acidic media, and it is desirable to find the acetal, the protected alcohol, stable toward acidic conditions.

In this communication, we wish to report on a novel acetal-type protective group for alcohols which is rather resistant to acidic hydrolysis. Since the introduction of an electron-withdrawing substituent on the acetal carbon increases the stability toward acidic conditions, the protection of hydroxyl groups with 2-benzyloxy-3-fluoro-1-propene (2) in place of 2-benzyloxy-1-propene was studied.

The preparation of 2-benzyloxy-3-fluoro-1-propene (2) was successfully achieved starting from 2-benzyloxy-1,3-difluoropropane (1)[2] according to the following procedure (Scheme 1): To a solution of potassium *t*-butylate (12.3 g, 110 mmol) in *t*-butyl alcohol (100 ml) was added a benzene solution (80 ml) of 2-benzyloxy-1,3-difluoropropane (1, 17.2 g, 93 mmol) over 1 h under reflux. After refluxing for additional 2 h, the reaction mixture was cooled and water was added. The mixture was extracted with chloroform and organic layer was dried over sodium sulfate. The solvent was evaporated and *t*-butyl alcohol was removed by azeotropic distillation with cyclohexane. 2-Benzyloxy-3-fluoro-1-propene (2, 13.3 g, 87%) was isolated by further distillation under reduced pressure; bp 108-111 °C/22 mmHg; ^{1}H-NMR (CCl_4) δ 4.15 (2H, s), 4.57 (2H, d, J = 46 Hz), 4.62 (2H, s), 7.12 (5H, s); IR (neat) 1640, 1500, 1455, 1295, 740, 695 cm^{-1}.

Scheme 1.

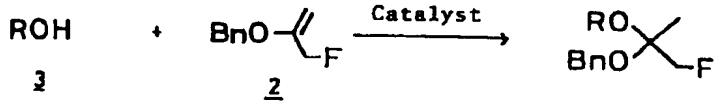


1 → 2 87% Bn = $PhCH_2$-

Then, an alcohol (3) was treated with 2-benzyloxy-3-fluoro-1-propene (2) in the presence of various catalysts such as protic acids and palladium complexes.[3] And it was found that the desired acetal (4) was obtained in a high yield under very mild conditions when a catalytic amount of dichloro(1,5-cyclooctadiene)-palladium(II) was used in acetonitrile (Table 1).

Scheme 2.

Bn = $PhCH_2$-



3 2 4

Table 1. COD = cyclooctadiene

Catalyst		R-	Solvent	Temp.	Time	Yield / %
0.1 eq.	H_2SO_4	$Ph(CH_2)_3$-	Et_2O	rt	1 h	72
0.1 eq.	FSO_3H	$Ph(CH_2)_3$-	Et_2O	rt	1 h	89
0.01 eq.	$ClSO_3H$	$Ph(CH_2)_3$-	Et_2O	rt	1 h	99
0.1 eq.	$PdCl_2$(COD)	$Ph(CH_2)_3$-	CH_3CN	rt	1 d	quant.
0.1 eq.	$PdCl_2$(COD)	$PhCO_2(CH_2)_3$-	CH_3CN	rt	1 d	95
0.1 eq.	$PdCl_2$(COD)	$PhCO_2(CH_2)_3$-	Benzene	refl	2 d	70
0.1 eq.	$PdBr_2$(COD)	$PhCO_2(CH_2)_3$-	CH_3CN	rt	1 d	87
0.1 eq.	$PdCl_2(PhCN)_2$	$PhCO_2(CH_2)_3$-	CH_3CN	rt	1 d	82

Several alcohols were protected with 2 and the results are listed in Table 2. As shown in entry 4, the diol having both a primary and a secondary alcoholic hydroxyl groups gave the product in which only a primary alcoholic hydroxyl group was selectively protected.

The regeneration of the parent alcohol (3) from the acetal (4) was successfully carried out by catalytic hydrogenation under neutral conditions (5% Pd-C, EtOH, room temperature, 1 atm, 12 – 24 h, Table 2).

Next, the stability of the fluoroacetal (4) toward acidic conditions (aqueous AcOH - THF, room temperature) was compared with benzyl acetal (6) and t-butyldimethylsilyl ether (7). And it was found that 4 is not hydrolyzed, while 8 and 9 are readily converted to the parent alcohol (3) indicating that the introduction of fluoromethyl group on the acetal carbon much increased the stability of the acetal in acidic media (Scheme 4). In addition, the fluoroacetal (4) is not affected by reducing hydride reagents [$LiAlH_4$, i-Bu_2AlH], organometallics (n-BuLi, n-BuMgBr), or alkaline aqueous solution [1 M aq. NaOH - THF (1 : 1)].

Typical experimental procedure for the protection of alcohols is as follows: Under an argon atmosphere, to a mixture of an alcohol (0.4 mmol) and dichloro(1,5-cyclooctadiene)palladium(II) (0.04 mmol) in acetonitrile (5 ml) was added 2-benzyloxy-3-fluoro-1-propene (0.8 mmol) in acetonitrile (2 ml) at room temperature. After stirring for 24 h, several drops of pyridine were added and the mixture was

Scheme 3.

Bn = $PhCH_2$-

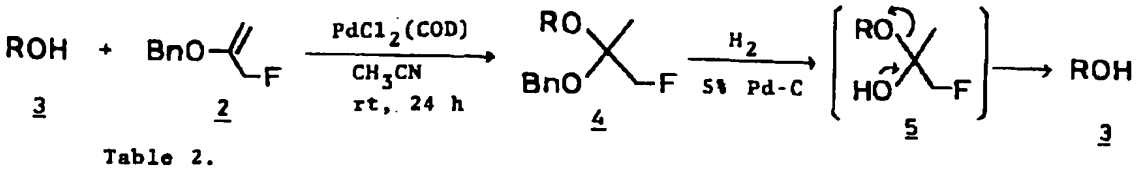
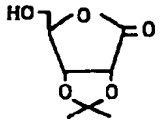
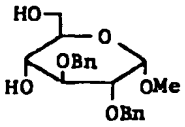
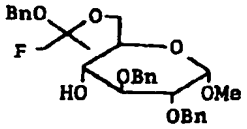
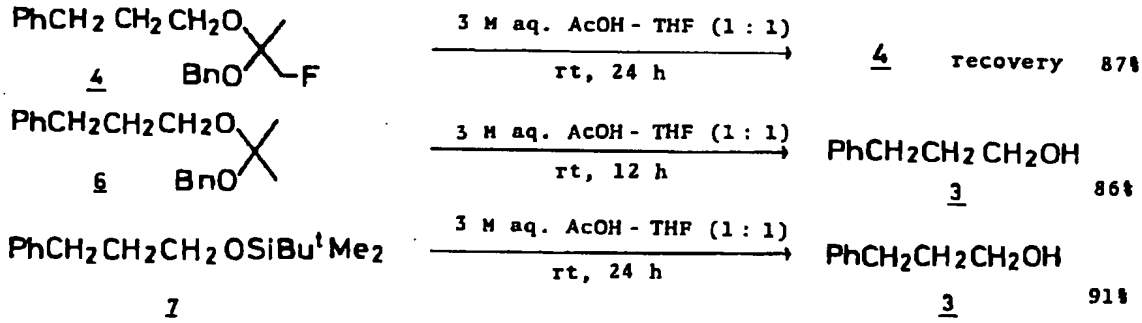


Table 2.

Entry	ROH	Protection Yield of 4 /%	Deprotection Yield of 3 /%
1	$PhCH_2CH_2CH_2OH$	quant. (99)	98
2	$PhCO_2CH_2CH_2CH_2OH$	95 (95)	quant.
3		89 (83)	99
4		93[b] (71)	—

a) Yields in parentheses were obtained when $ClSO_3H$ was used in Et_2O as a catalyst instead of $PdCl_2(COD)$.
b) The product is 

Scheme 4.



diluted with ether. The resulting insoluble materials were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel) to give the desired acetal.

It shoud be noted that 2-benzyloxy-3-fluoro-1-propene (2) is a new and useful

acetal-type protective reagent for hydroxyl groups with the following characteristics; 1) both protection and regeneration of alcohols are carried out under very mild conditions; 2) procedures for protection and deprotection are simple without extraction; 3) a primary alcoholic hydroxyl group is selectively protected; 4) the acetal, the protected alcohol, is rather stable to acidic conditions.

References

1) T. Mukaiyama, M. Ohshima, and M. Murakami, Chem. Lett., 1984, 265.

2) 2-Benzyloxy-1,3-difluoropropane (1) was prepared from 1,3-difluoro-2-propanol[4] according to the following procedure: To a suspension of sodium hydride (3.6 g, 0.15 mol), potassium fluoride (6.0 g, 0.10 mol), and benzyl bromide (51 g, 0.30 mol) in dimethylformamide (DMF, 120 ml) was added a DMF solution (30 ml) of 1,3-difluoro-2-propanol (14.4 g, 0.15 mol) at 0 °C. Then the temperature was raised to room temperature and the mixture was stirred for 24 h. After adding water to the mixture, organic materials were extracted with ether and the ethereal extracts were dried over sodium sulfate. The solvent was removed and 2-benzyloxy-1,3-difluoropropane (1, 17.2 g, 62%) was obtained by distillation under reduced pressure; bp 117-120 °C/20 mmHg; ^{1}H-NMR ($CDCl_3$) δ 3.47-3.87 (1H, m), 4.40 (4H, dd, J = 4, 46 Hz), 4.53 (2H, s), 7.17 (5H, s); IR (neat) 1500, 1455, 740, 700 cm^{-1}.

3) Utimoto et al. reported that alcohols add to alkenyl ethers such as 2,3-dihydrofuran and 3,4-dihydro-2H-pyran under the action of dichlorobis-(benzonitrile)palladium(II): K. Utimoto, Pure Appl. Chem., 55, 1845 (1983); S. Fujikura, K. Utimoto, and H. Nozaki, submitted to Tetrahedron Lett.

4) E. D. Bergmann and S. Cohen, J. Chem. Soc., 1958, 2259.

(Received February 9, 1984)